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Applicant	: Francisco Romero et al.	Art Unit	: 1614
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Title : NEW CYTOTOXIC DEPSIPEPTIDES

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REQUEST FOR CORRECTED PUBLICATION

Applicants hereby request a Corrected Publication pursuant to 37 C.F.R. §1.221(b). The above-identified application, which published on April 12, 2007 as Publication Number US 2007/0082878 A1, contained the following errors that were created by the USPTO:

On Page 3

On page 3, column 1, paragraph 33, end of line 6 "N_2" should be replaced with --NO_2--. This correction is supported in the application as filed on page 8, second paragraph, line 5.

On page 9

On page 9, column 2, paragraph 94, line 10 "$\beta T1=T_{p1}-T_{01}$" should be replaced with --$\Delta T1=T_{p1}-T_{01}$--. This correction is supported in the application as filed on page 30, first complete paragraph, line 9.

No fee is believed to be due, inasmuch as all errors were created by the USPTO, and expiration of the two month period to request a corrected publication, June 12, 2007, has not passed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: May 11, 2007

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(54) CYTOTOXIC DEPSIPEPTIDES

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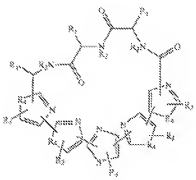
C12P 17/00 (2006.01)

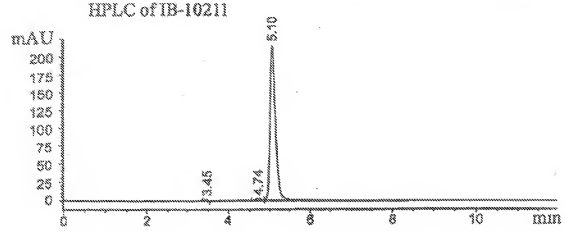
(52) U.S. Cl. 514/183; 540/455; 435/117; 435/252.35; 514/366

(57) ABSTRACT

Compounds of general formula (1) wherein R_1, R_{1a}, R_3 are as defined and R_4 groups are each independently selected from NR_4, O and S; are of use in treatment of cancers.

(I)




HPLC of IB-10211
mAU
200
175
150
125
100
75
50
25
0
3.45
4.74
5.10
0
2
4
6
8
10
min

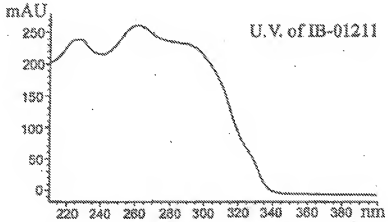

mAU
250
200
150
100
50
0
U.V. of IB-01211
220 240 260 280 300 320 340 360 380 nm

Fig1

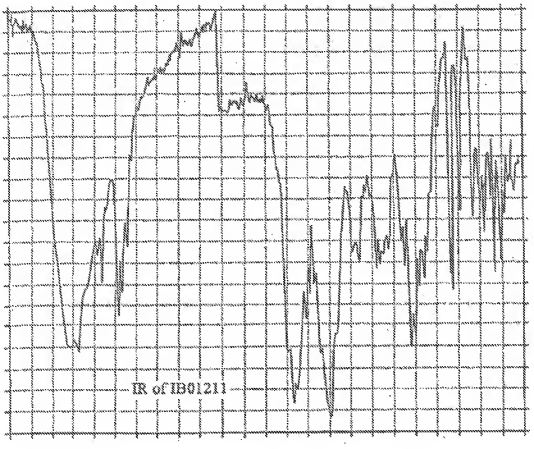


Fig.2

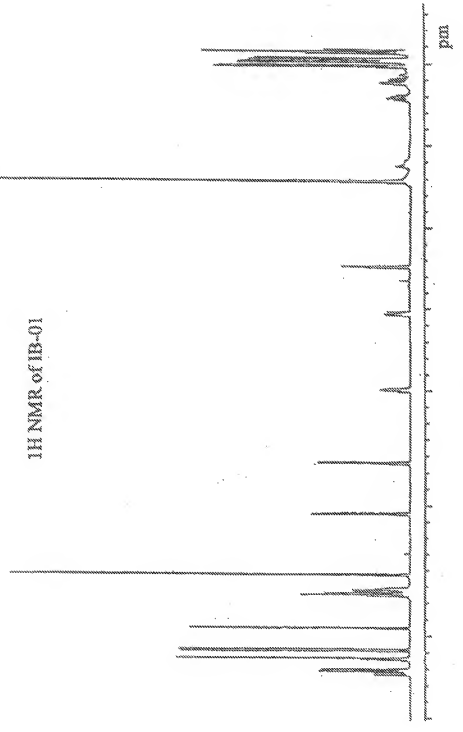


Fig.3

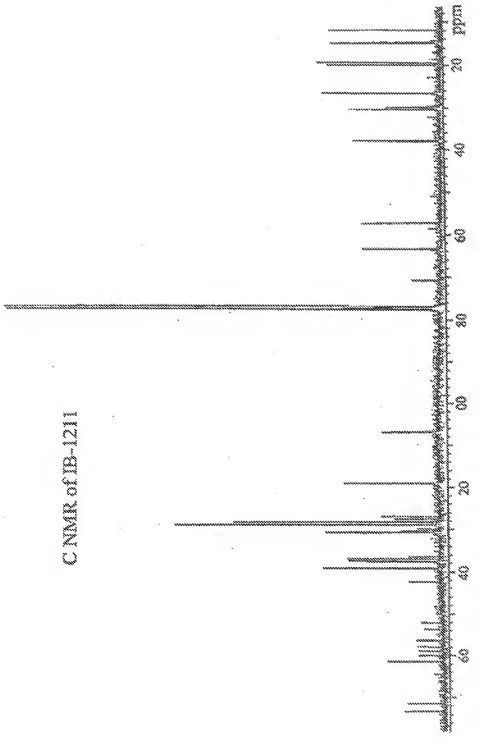


Fig.4

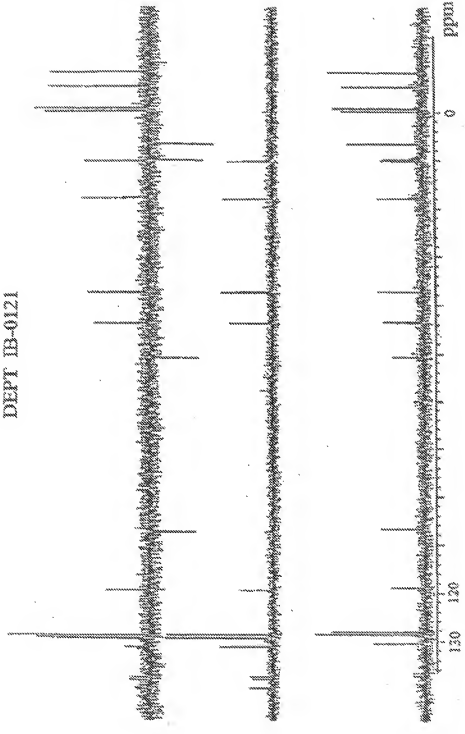


Fig.5

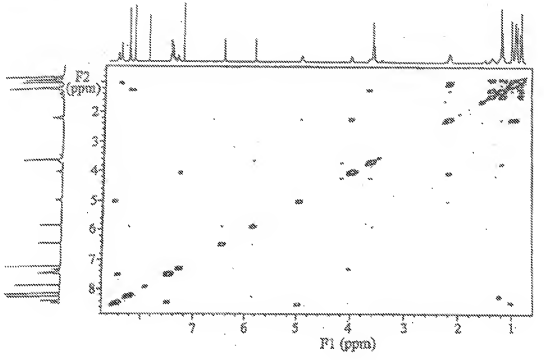


Fig.6

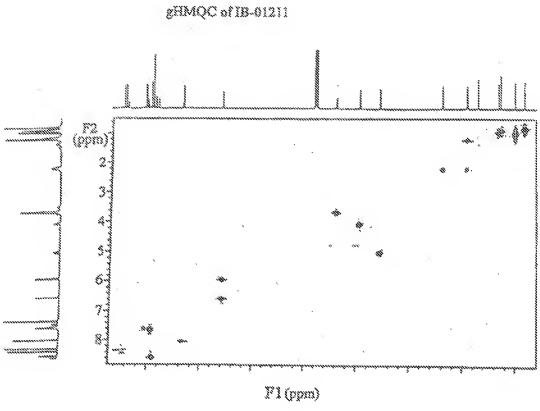


Fig.7

gHMBC IB-01211

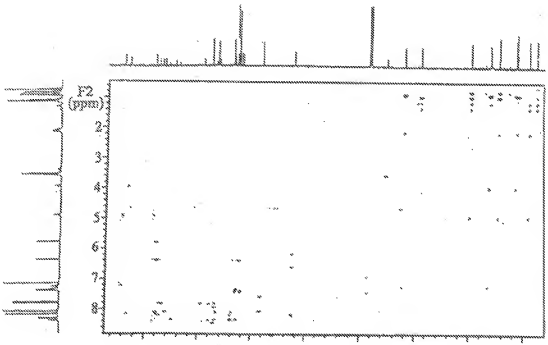


Fig.8

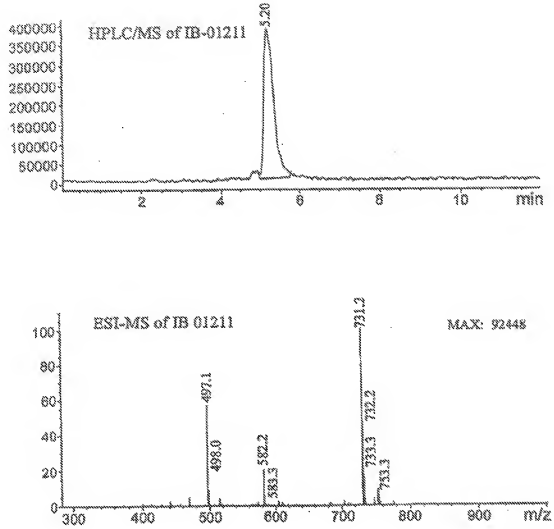

HPLC/MS of IB-01211
5.20
400000
350000
300000
250000
200000
150000
100000
50000
0
2
4
6
8
10
min
ESI-MS of IB 01211
MAX: 92448
731.2
497.1
732.2
498.0
582.2
733.3
583.3
753.3
100
80
60
40
20
0
300
400
500
600
700
800
900
m/z

Fig.9

CYTOTOXIC DEPSIPEPTIDES

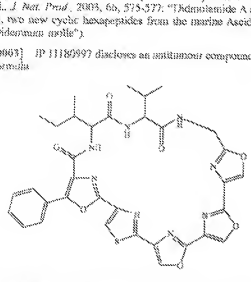
FIELD OF THE INVENTION

[0001] The present invention relates to new depsipeptide compounds, pharmaceutical compositions containing them and their use as antitumoural agents.

BACKGROUND OF THE INVENTION

[0002] Several cyclic peptides obtained from marine organisms have been disclosed (see for example Rudi A. et al., *J. Nat. Prod.*, 2003, 66, 575-577: "Didmolamide A and B, two new cyclic hexapeptides from the marine Ascidian *Didemnum molle*").

[0003] JP 11180997 discloses an antitumour compound of formula



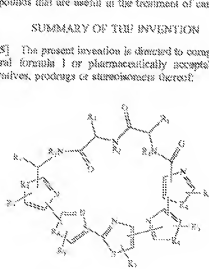
which is obtained from *Streptomyces nobilis*. Its IC_{50} in Huta 83 cells is 14 nM

[0004] Cancer is a leading cause of death in animals and humans. Several efforts have been and are still being undertaken in order to obtain an antitumour agent active and safe to be administered to patients suffering from a cancer. The problem to be solved by the present invention is to provide compounds that are useful in the treatment of cancer.

SUMMARY OF THE INVENTION

[0005] The present invention is directed to compounds of general formula I or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof;

(I)



wherein

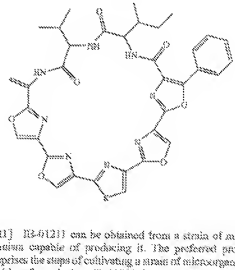
[0006] R_1 groups are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, nitro, azido, substituted or unsubstituted alkyl, substituted or unsubstituted alkyldiene, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group and substituted or unsubstituted acyl;

[0007] R_2 groups are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, nitro, azido, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group and substituted or unsubstituted acyl;

[0008] R_4 groups are each independently selected from NR_2, O and S; and

[0009] R_5 groups are each independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkoxy and substituted or unsubstituted acyl.

[0010] The present invention also relates to the obtaining of the compounds of formula I, including the compound we call IB-01211 which is of formula:

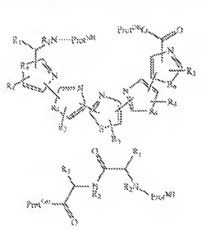


[0011] IB-01211 can be obtained from a strain of microorganism capable of producing it. The preferred process comprises the steps of cultivating a strain of microorganisms capable of producing IB-01211 in an aqueous nutrient medium with assimilable carbon and nitrogen sources and salts, under controlled submerged aerobic conditions, and then recovering and purifying the compound from the cultured broth

[0012] Other compounds of this invention can be derived from IB-01211, or can be made by synthesis. Thus, the oxazole/thiazole/imidazole fragment of the compounds of the present invention can be synthesized by using the teaching of the following literature. Panek J. S. et al., "Studies directed toward the synthesis of Ulapualide A. Asymmetric Synthesis of the C8-C25 tris-oxazole frag-

ment" *J. Org. Chem.* 1996, 61, 6496-6497; Panek J. S. et al. "Studies directed toward the total synthesis of kabiramide C: asymmetric synthesis of the C7-C19 fragment" *Tetrahedron Lett.* 1998, 39, 6143-6146; Panek J. S. et al. "Synthesis of the fully functionalized tris-oxazole fragment found in metabolites derived from marine organisms" *Tetrahedron Lett.* 1997, 38, 5445-5448; Pattenden G. "Synthetic studies with natural oxazoles and thiazoles" *J. Heterocyclic Chem.* 1992, 29, 607-618; Pattenden G. et al. "Synthesis of the tris-oxazole ring system of ulapualides" *Synlett.* 1990, 36-37; Kiso Y. et al. "Convergent synthesis of (−)-mirabazole C using a chloroimidazolidium coupling reagent, CIP" *J. Org. Chem.* 1996, 61, 3350-3357; Wipf P. et al. "Total synthesis of (−)-thiangazole and structurally related polyazoles" *J. Org. Chem.* 1995, 60, 7224-7229; Wipf P. et al. "A new synthesis of highly functionalized oxazoles" *J. Org. Chem.* 1993, 58, 3604-3606. Once the oxazole/thiazole/imidazole fragment is synthesised the aminoacidic fragment is introduced by using conventional methods of peptide synthesis already known by the skilled person in the art.

[0013] Thus, compounds of formula I including IB-01211 can be made by coupling of the following components:



where R_1, R_2, R_3, R_4 are as defined, $Prot^{OH}$ is an optional protecting group for hydroxy, and $Prot_{NH}$ is an optional protecting group for amino. As appropriate, the respective protecting groups can be replaced by other reactive groups to encourage the desired coupling, which typically takes place sequentially first to join the oxazole/thiazole/imidazole fragment to one end of the amino acidic fragement, and then to close the ring.

[0014] In another aspect, the present invention is directed to pharmaceutical compositions containing a compound of formula I or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof, together with a pharmaceutically acceptable carrier or diluent.

[0015] In another aspect, the present invention is also directed to the use of compounds of formula I or pharmaceutically acceptable salts, derivatives, prodrugs or stereoisomers thereof in the treatment of cancer, or in the preparation of a medicament for the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1. HPLC/UV chromatogram and UV spectrum of purified IB-01211

[0017] FIG. 2. IR spectrum of purified IB-01211

[0018] FIG. 3. ^1H NMR spectrum of purified IB-01211

[0019] FIG. 4. ^{13}C NMR spectrum of purified IB-01211

[0020] FIG. 5. DEPT spectrum of purified IB-01211

[0021] FIG. 6. COSY 45 spectrum of purified IB-01211

[0022] FIG. 7. HMQC spectrum of purified IB-01211

[0023] FIG. 8. HMBC spectrum of purified IB-01211

[0024] FIG. 9. HPLC/MS chromatogram and ESI-MS spectrum of purified IB-01211

DETAILED DESCRIPTION OF THE INVENTION

[0025] The present invention relates to compounds of general formula I as defined above.

[0026] In these compounds the substituents can be selected in accordance with the following guidance:

[0027] Alkyl and alkoxy groups preferably have from 1 to 12 carbon atoms. One more preferred class of alkyl groups has 1 to about 8 carbon atoms, yet more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methyl, ethyl, propyl including isopropyl, and butyl including isobutyl, sec-butyl and tert-butyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

[0028] Alkylidene groups may be branched or unbranched and preferably have from 1 to 12 carbon atoms. One more preferred class of alkylidene groups has from 1 to about 8 carbon atoms, yet more preferably from 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methylidene, ethylidene and propylidene including isopropylidene are particularly preferred alkylidene groups in the compounds of the present invention.

[0029] Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred. In a general sense, we include alkylidene within alkenyl, they both being substituents with a double bond.

[0030] Suitable aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred aryl groups include substituted or unsubstituted phenyl, naphthyl, biphenyl, phenanthryl and anthracyl.

[0031] Suitable acyl groups include alkanoyl groups which have from 2 to about 12 carbon atoms, more preferably from 2 to about 8 carbon atoms, still more preferably from 2 to about 6 carbon atoms, even more preferably 2

carbon atoms. Other aryl groups include alkenylaryl, alkynylaryl, arylaryl, heterocyclylaryl.

[0032] Suitable heterocyclic groups include heteroaromatic and heterocyclyclic groups. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyridonyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazol. Suitable heterocyclyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl groups.

[0033] The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', SR, SOR', SO_2R', NO_2, NHR', $N(R')_2$, $NHCOR'$, $N(COR')_2$, $NHSO_2R'$, CN, halogen, $C(=O)R'$, CO_2R', $OC(=O)R'$ wherein each of the R' groups is independently selected from the group consisting of H, OH, NO_2, NH_2, SH, CN, halogen, $C(=O)H$, $C(=O)$alkyl, CO_2H, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_1-C_{18} alkoxyl and substituted or unsubstituted aryl.

[0034] Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I.

[0035] The term "pharmaceutically acceptable salts, derivatives, prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate, hydrate or any other compound which, upon administration to the patient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts, prodrugs and derivatives can be carried out by methods known in the art.

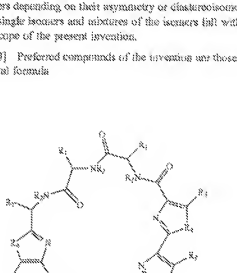
[0036] For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate phosphate, and organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and p-toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example sodium, potassium, calcium and ammonium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkylenethanolamine, triethanolamine and basic aminoacids salts.

[0037] The compounds of the invention may be in crystalline form either as free compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

[0038] Any compound that is a prodrug of a compound of formula I is within the scope and spirit of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester derivative.

[0039] The compounds of the present invention represented by the above described formula I may include enantiomers depending on their asymmetry or diastereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

[0040] Preferred compounds of the invention are those of general formula



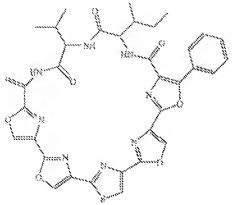
(II)

[0041] wherein R_1, $R_{1'}$ R_3 and R_4 groups have the same meaning as defined above

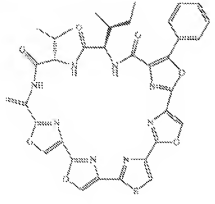
[0042] Preferred R_1 groups are substituted or unsubstituted alkyl and substituted or unsubstituted alkylidene, more preferred are substituted or unsubstituted C_1-C_6 alkyl and substituted or unsubstituted C_1-C_6 alkylidene, still more preferred are isopropyl, sec-butyl and methylene

Preferred R_3 groups are H and substituted or unsubstituted alkyl, and more preferred is H. Preferred R_4 groups are H and substituted or unsubstituted aryl, and more preferred are H and phenyl. Preferred R_2 group is O.

[0043] One particularly preferred compound of formula I is compound H-01211.



[0044] The preferred stereochemistry of the above mentioned compound is the following



[0045] Compound H-01211 is preferably obtained from an actinomycete, named strain BS7-008. A culture of this strain has been deposited in the Colección Española de Cultivos Tipo at the University of Valencia, in Spain, under the accession number CECT 3358. This deposit has been made under the provisions of the Budapest Treaty.

[0046] The microorganism strain BS7-008 is phylogenetically close to *Thermoactinomyces* genus. The organism was isolated from an unidentified marine sponge. The taxonomic methods were as follows

1. Colonial Morphology.

[0047] ISP Media No 2, 4, 5 and 6: Shirling B. E., and D. Gottlieb, *Int. J. Syst. Bacteriol.* 16:313, 1966

[0048] ATCC Medium No 172: American Type Culture Catalog 17th edition, 1989 Rockville, Md. U.S.A.

[0049] Czapek Agar Difco

[0050] Bennet Agar, Wakamoto, S. A *The Actinomycetes* vol.II:331, 1961

[0051] All media were supplemented with 50% ASW

2. Physiological Characteristics:

[0052] ISP medium n°1, Shirling and Gottlieb.

[0053] NaCl resistance: ATCC 172 with 0, 2, 4, 5, 7 and 10% NaCl.

[0054] Carbon utilization: ISP-9, Shirling and Gottlieb

3. Fatty Acids Analysis.

[0055] Shirling B. E., and D. Gottlieb. *Int. J. Syst Bacteriol.* 16:313, 1966

4. Whole Cell Sugar Analysis:

[0056] Guerrant G. O., and C. W. Moss. *Anal. Chem.* 56:633, 1984

5. Diaminopimelic Acids Analysis:

[0057] Hasegow T., M. Takizawa, and S. Tanida. J. Gen Appl. Microbiol. 29:319, 1983

[0058] All cultures were incubated at 28° C. and records of results were made weekly up to 21 days.

[0059] A description of the organism is as follows.

Morphology:

[0060] After 21 days at 28° C., growth was observed in ISP2 and 172 broth supplemented with artificial sea water (ASW). No aerial mycelium was formed. Substrate mycelium was branched. Spores are formed both in solid and liquid media as endospores.

Physiology:

[0061] No diffusible pigments were formed by strain BS7-008, neither on solid or liquid media. The optimum of NaCl concentration in the medium for optimal growth was in the 4%-7% range. Growth did not occur at 28° C. in the absence of salt even in rich media compositions as ATCC's 172 medium. The optimum growth temperature range was between 28° C.-40° C.

[0062] The strain BS7-008 can utilize glucose, melibiose, xylose, and ethanol as carbon sources. Growth was poor on fructose, sucrose, rhamnose, and galactose. The organism did not grow on arabinose, mannose or myo-inositol.

Chemical Composition:

[0063] Aminoacids:

[0064] meso-2,6-diaminopimelic acid was present in the whole hydrolysated cell of strain BS7-008

Fatty Acids Composition:

[0065] The mayor fatty acids were identified as i-15:0, a-15:0, 15:0, i-16:0, i-17:1, i-17:0, and a-17:0. The fatty acids composition of strain BS7-008 and other actinomycete strains it is the following table, where the composition is given as percentage of total fatty acids content.

	%							
	13:0	i-14:0	14:0	i-15:0	15:0	i-16:1	i-16:0	
BS7-008	<1	<1	<1	<1	64.2	0.59	1.36	<1
STAURIS	<1	6.32	<1	9.88	2.92	<1	5.50	35.29
SPAMETH	1.25	10.04	<1	1.86	<1	0.39	<1	15.51

-continued

SPVIRIDO	<1	4.06	1.10	18.94	2.71	4.89	<1	26.44
AMCITRE	<1	<1	3.18	<1	<1	1.03	<1	6.57
AFBRAZIL	<1	2.15	<1	15.46	10.91	2.16	<1	18.07
AMPDIGIT	<1	13.57	<1	31.21	9.98	<1	2.87	34.25
AMYORIE	<1	3.40	3.37	19.94	4.64	1.17	<1	13.85
MNCHALC	<1	3.68	<1	8.93	2.29	1.53	1.15	38.25
MNECHCA	<1	1.17	<1	4.97	1.24	2.81	<1	30.88
MNFUSCA	<1	<1	<1	26.56	6.53	<1	<1	8.58
SACCAER	<1	3.08	1.35	14.41	8.62	1.04	5.68	20.57
NOAFRI	1.31	3.40	3.35	4.62	<1	7.46	3.96	22.14
MTSALMO	<1	3.12	1.78	6.73	<1	7.83	7.53	23.58
MTRUBRA	<1	1.46	1.38	4.12	<1	3.41	7.27	25.60
MTROSEO	2.03	1.98	4.14	3.86	<1	9.03	3.62	12.71
AMROSEO	<1	2.19	1.26	6.73	1.08	6.94	1.40	22.21
MTFERRU	1.13	1.85	1.19	1.98	<1	6.43	4.12	21.50

	16:0	i-17:1	i-17:0	a-17:1	a-17:0	17:1	17:0
ES5-608	4.32	<1	<1	14.68	4.14	1.48	<1
STALBUS	<1	3.75	1.28	3.38	8.80	<1	<1
SPAMETH	5.63	8.67	1.68	<1	<1	24.62	9.40
SPVIRIDO	<1	4.43	<1	2.60	1.38	11.36	8.58
AMCITRE	12.62	<1	<1	<1	<1	<1	1.16
AFBRAZIL	2.75	3.79	<1	2.59	9.64	11.18	2.82
AMPDIGIT	<1	1.68	<1	1.28	5.68	4.39	1.64
AMYORIE	5.29	18.41	<1	2.89	4.44	3.09	2.73
MNCHALC	<1	1.88	1.69	2.22	2.25	5.43	6.95
MNECHCA	<1	2.29	1.63	4.11	1.68	12.15	4.90
MNFUSCA	<1	<1	7.30	11.89	13.25	2.90	3.37
SACCAER	12.84	6.16	4.55	2.20	5.31	2.02	<1
NOAFRI	2.69	5.15	2.35	<1	<1	8.15	4.75
MTSALMO	1.20	3.97	3.01	<1	3.07	11.58	5.53
MTRUBRA	2.63	3.87	2.17	1.08	<1	8.88	4.97
MTROSEO	2.66	6.95	1.17	<1	<1	13.91	4.46
AMROSEO	2.21	3.61	2.74	1.03	<1	16.97	4.33
MTFERRU	2.32	2.36	<1	<1	<1	25.51	5.71

	i-18:1	i-18:0	cis-18:1	18:0
ES5-608	<1	<1	<1	<1
STALBUS	<1	1.09	<1	<1
SPAMETH	7.11	<1	4.60	1.16
SPVIRIDO	7.48	<1	<1	1.16
AMCITRE	<1	<1	14.25	2.82
AFBRAZIL	<1	<1	3.38	1.06
AMPDIGIT	<1	1.76	7.00	1.54
AMYORIE	<1	<1	6.21	3.04
MNCHALC	34.58	1.31	1.28	2.68
MNECHCA	7.23	<1	10.05	1.09
MNFUSCA	3.50	<1	2.33	1.94
SACCAER	<1	<1	<1	1.43
NOAFRI	17.03	<1	<1	1.25
MTSALMO	17.04	<1	<1	<1
MTRUBRA	15.44	1.25	<1	1.61
MTROSEO	18.67	<1	1.77	<1
AMROSEO	17.86	<1	<1	<1
MTFERRU	12.13	1.27	1.40	<1

ES5-608 = strain ES5-608;
AMCITRE = *Actinomadura citrea* DSM 43461;
AMPDIGIT = *Ampullariella digitata* ATCC 15349;
AMROSEO = *Actinomadura roseoviolacea* DSM 43144;
AMYORIE = *Amycolatopsis orientalis* DSM 40040;
AFBRAZIL = *Actinoplanes brasiliensis* ATCC 25844;
MNCHALC = *Micromonospora chalcea* ATCC 31395;
MNECHCA = *Micromonospora echinospora calichensis* NRRL 15839;
MNFUSCA = *Micromonospora fusca* NRRL B-3298;
MTFERRU = *Microtetraspora ferruginea* DSM 43553;
MTROSEO = *Microtetraspora roseola* ATCC 33579;
MTRUBRA = *Microtetraspora rubra* ATCC 27031;
MTSALMO = *Microtetraspora salmonea* ATCC 33580;
NOAFRI = *Nocardiopsis africana* DSM 43748;
SACCAER = *Saccharothrix aerocolonigenes* NRRL B-3298;
SPAMETH = *Streptosporangium amethystogenes* DSM 43179;
SPVIRIDO = *Streptosporangium viridogriseum* ATCC 25242;
STALBUS = *Streptomyces albus* DSM 40313

Sugar:

The whole cell sugar pattern did not show a specific profile.

Phylogenetic Analysis.

[0066] Partial sequence of 16S rDNA was performed following standard procedures. The DNA of the organism was extracted after homogenization under liquid nitrogen. The 16S rDNA gene was amplified by the polymerase chain reaction using the eubacterial primers 27f and 1492r. The partial sequences were obtained using the primers 357r, 926r, and 1492r. All the primers used in this work were described by Lane, D. J. *Nucleic acid techniques in bacterial systematics*: 115, 1991. The partial sequence obtained was:

GCGGACGGGTGAGTAACGCGTGGGCAACCTGCCCTGCAAGATCGGGATAAC
CCCGGCAAACCGGAGCTAATACCGAATAATCTTTTTCCTCGCATGCGAG
GAAGTAAAAGAAGGTTTCGGCCTTCACTTGCAGATGGGCCCGCGGCGCAT
TAGCTAGTTGGTGGGGTAGAGGCTTACCAAGGCGACGACGCGTAGCCGAC
CTGAGAGGGTGATCGGCCACACTGGGACTGAGACACGGCCCAGACTCCTA
CGGGAGGCAGCAGTGGGGAATTTTCCGCAATGGGCGAAAGCCTGACGGAG
CAACGCCGCGTGAGTGAGGACGGTTTTCGGATTGTAAAGCTCTTTCCTTT
CCGATGAAGCAGCAAGCAGAGGAAATGCTCTTTGTGTGACGGTAGGAAAGA
AGAAAGCCCCGGCTAACTACGTGCCAGCAGCCGCGGTAATACGTAGGGCG
CAAGCGTTGTCCGGAATTATTGGGCGTAAAGCGCGCGCAGGCGGGCTGTT
AAGTCGGATGTGAAAGCCCACGGCTCAACCGTGGAAGGGCATCCGAAACT
GGCGGGCTTGAGTGCAGAAGAGGAGACTGGAATTCCCGGTGTAGCGGTGG
AATGCGTAGAGATCGGGAGGAACACCAGTGGCGAAGGCGGCTCTCTGGGC
TGCAACTGACGCTGAGGCGCGAAAGCGTGGGGAGCGAACAGGATTAGATA
CCCTGGTAGTCCACGCCGTAAACGATGAGTGCTAGGTGTTGGGGGTGTCA
TGCCTCTGTGCCGAAGCTAACGCAATAAGCACTCCGCCTGGGGAGTACG
GCCGCAAGGCTGAAACTCAAAGGAATTGACGGGGGCCCGCACAAGCGGTG
GAGCATGTGGTTTAATTCGAAGCAACGCGAAGAACCTTACCAGGGCTTGA
CATCCTTCTGATCGGCTTAGAGATCAAGCTTTCTTTCGGAGCAGAAGTGA
CAGGTGGTGCATGGTTGTCGTCAGCTCGTGTCGTGAGATGTTGGGTTAAG
TCCCGCAACGAGCGCAACCCTTATGGTTAGTTGCCAGCATTAAGTTGGGC
ACTCTAACGGGACAGCCGGTGAAAGCCGGAGGAAGGTGGGGATGACGTCA
AGTCATCATGCCCCTTATGTCCTGGGCCACACACGTGCTACAATGGCTGG
TACAACGGGTAGCGAAGCTGCGAAGTGGAGCCAATCCCTAAAAACCAGTC
TCAGTTCGGATCGTAGTCTGCAACTCGACTACGTGAAGCTGGAATCGCTA
GTAATCGCGGATCAGCATGCCGCGGTGAATACGTTCCCGGGCCTTGTACA
CACCGCCCGTCACACCACGAGAGTTTGCA

[0067] This sequence was confronted with the Gene Bank depository using the Blasta algorithm. The phylogenetic studies were performed using the Phylip package developed by Felsenstein, J. *Cladistics* 5:164, 1989. A consensus phylogenetic tree was constructed after bootstrapping the

sample. Strain ES7-008 was grouped with the *Thermoactinomycer* group. A differentiating trait of strain ES7-008 with *Thermoactinomycetes* is a lack of aerial mycelium and the need of salt for growth.

Fermentation

[0068] ES7-008 produces compound IB-01211 when it is cultured under controlled conditions in a suitable medium. This strain is preferably grown in an aqueous nutrient medium, under aerobic and mesophilic conditions, preferably at 28° C.-40° C. and at a pH ranging between 6.0 and 8.0. A wide variety of liquid culture media can be used for the cultivation of the organism. Useful media are those that include an assimilable carbon source, such as starch, dextrin, sugar molasses, glucose, an assimilable nitrogen source such as protein, hydrolysed protein, defatted meals, corn steep, and useful inorganic anions and cations such a sodium, magnesium, potassium, ammonium, sulfate, chloride, phosphate, carbonate. Trace elements may be added also. Aeration is preferably achieved by supplying air to the fermentation medium. Agitation is provided by a mechanical impeller. Conventional fermentation tanks have been found to be well suited for carrying out the cultivation of this organism. The addition of nutrients and pH control as well as antifoaming agents during the different stages of fermentation may be needed for increasing production and avoiding foaming.

[0069] Compound IB-01211 can be produced starting with a frozen lyophilized mycelium of ES7-008. A mycelial mass is obtained by culturing the initial cells in shake flasks with a culture medium containing some of the ingredients described above at mesophilic temperatures and in aerobic conditions. This step may be repeated several times as needed and the material collected will be used as an inoculum to seed one or several fermentation tanks with the appropriate culture medium. If it is desired these tanks can be used for developing the inoculum or for the production stage, depending on the broth volume needed. Sometimes the production medium may be different than the ones used for inoculum development. Typical media are disclosed that can be used for inoculum development and for production of IB-01211 are in the following table.

Inoculum medium		Production medium	
Soybean flour	5 g	Yeast	5 g
Glucose	1 g	Peptone	3 g
Starch	20 g	Soybean flour	5 g
Beef extract	5 g	Soybean meal	15 g
Yeast extract	5 g	Yeast extract	5 g
Tryptone	5 g	Tryptone	3 g
$CaCO_3$	4 g	$CaCO_3$	4 g
NPT	5 g	NaCl	4 g
Na_2SO_4	7 g	Na_2SO_4	4 g
KCl	0.5 g	KCl	0.5 g
$MgCl_2$	5 g	$MgCl_2$	2 g
H_2O	To 1 liter	H_3PO_4	0.5 g
		H_2O	To 1 liter

[0070] Production of IB-01211 can be monitored by whole broth assay against murine leukemia P-388 or by HPLC

[0071] Compound IB-01211 can be isolated from the mycelial cake by extraction with a suitable mixture of solvents such as $CHCl_3$:CH_3OH:H_2O. The activity is concentrated in the lower layer. The extracts from two repeated extraction can be combined and evaporated to dryness in vacuo.

[0072] Separation and purification of IB-01211 from the crude active extract can be performed using the proper combination of conventional chromatographic techniques.

[0073] Fractionation can be guided by the antitumor activity of fractions, by TLC visualized with vanillin in concentrated H_2SO_4 or by analytical HPLC with photodiode-array and MS detector. HPLC analysis is performed at room temperature using an analytical column Symmetry C18 (5μ) and a MeOH:H_2O:HOAc 95:5:1 mobile phase at a flow rate of 0.5 ml/min and plotted at 260 nm. In this conditions the IB-01211 retention time is 5.1 min as it is shown in FIG. 9.

[0074] An important feature of the above described compounds is their bioactivity and in particular their cytotoxic activity. With this invention we provide novel pharmaceutical compositions of these compounds that possess cytotoxic activity, and their use as antitumour agents. Thus the present invention further provides pharmaceutical compositions comprising a compound of this invention or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof with a pharmaceutically acceptable carrier.

[0075] Examples of pharmaceutical compositions include any solid (tables, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) suitable composition for oral, topical or parenteral administration

[0076] Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

[0077] Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 1-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 1 to 4 weeks.

[0078] The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

[0079] The compounds and compositions of the invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time

EXAMPLES OF THE INVENTION

Example 1

Production of IB-01211

[0080] Inoculum development: a frozen culture of ES7-008 or a well grown slant culture (5% vol.) is used to seed 100 ml of a seed medium, as described in Table 1, that it is contained in a 250 ml shake flask. The flask is incubated during 48 h. A 2 l Erlenmeyer flask with 500 ml of the same medium is seeded with 10% vol. of the first stage inoculum. The flask is incubated during 48 h.

[0081] Fermentation step: 50 l of production medium, as described in Table 1, contained in a 75 l fermentation tank are seeded with 2.5 l of second stage inoculum. The fermentation is carried out during 96 h with 400 rpm agitation and an air flow of 0,5V/V.M.

Example 2

Isolation of IB-01211

[0082] 8.5 liters of whole harvested broth were filtrated to separate the biomass and other solids. The mycelia cake was extracted twice with a mixture solvent (2.4 l) of $CHCl_3$:CH_3OH:H_2O (2:1:1). The activity was concentrated in the lower layer. The organic solvent was concentrated and evaporated to dryness in vacuo to yield 4.8 g of crude extract.

[0083] The extract was applied to a silica gel VFC (vacuum flash chromatography) system, using a mixture of n-hexane-EtOAc and EtOAc-MeOH as eluting solvents. The fractions with antitumour activity, containing IB-01211 (900 mg) were eluted with EtOAc-MeOH 1:1, EtOAc-MeOH 1:3 and methanol. The active fractions were chromatographied twice with a silica gel column using $CHCl_3$-MeOH and EtOAc-MeOH mixtures as eluting solvents. The cytotoxic activity was detected in fractions eluted with $CHCl_3$-MeOH 96:4 in the first chromatography (200 mg of pure compound IB-01211) and in fractions eluted with EtOAc-MeOH 85:15-8:2 in the second chromatography (60 mg of pure compound IB-01211). Further purification with C18 reversed phase chromatography afforded 22 mg of pure compound IB-01211 eluted with MeOH

[0084] On the basis of detailed analysis of their various spectral characteristics, the pure compound was identified as IB-01211. The UV spectrum shows absorption at 225 nm, 265 nm and 290 nm as reported in FIG. 1. The infrared absorption spectrum is shown in FIG. 2 of the accompanying drawings. The ^{1}H NMR, ^{13}C NMR and DEPT spectra of IB-01211 are reported in FIG. 3, FIG. 4 and FIG. 5, respectively. The 2D NMR experiments COSY, HMQC and HMBC are reported in FIG. 6, FIG. 7 and FIG. 8, respectively. The ES-MS spectrum of IB-01211 displays a (M+Na) peak at 731 as reported in FIG. 9. ^{1}H and ^{13}C NMR data of compound IB-01211 are summarized in the following table.

Position	^{13}C (δ)	^{1}H (δ)
Isoleucine		
NH		8.46(d, 10.4)
αCH	57.3	4.99(dd, 10.5, 4.4)
βCH	37.8	2.27(m)
γCH$_2$	26.6	1.41(q, 7.5) 1.29(m)
γCH$_3$	14.9	1.05(d, 6.9)
δCH$_3$	11.9	0.87(t, 7.2)
CO	173.3	
Valine		
NH		7.73(d, 3.4)
αCH	60.6	4.06(dd, 8.7, 3.6)
βCH	30.3	2.23(m)
γCH$_3$	19.5	0.95(d, 6.8)
γCH$_3$	20.0	0.98(d, 6.8)
CO	171.2	
Oxazole (1)		
NH		8.28(bs)
αC	127.5	
βCH$_2$	108.8	6.30(s)
		5.88(s)
2-C	159.9	
4-C	130.5	
5-CH	138.3	8.2(s)
Oxazole (2)		
2-C	156.1	
4-C	136.4	
5-CH	126.9	8.16(s)
Thiazole		
2-C	157.8	
4-C	142.2	
5-CH	119.1	7.99(s)
Oxazole (3)		
2-C	158.6	
4-C	130.6	
5-CH	137.4	8.27(s)
Oxazole (4)		
2-C	152.0	
4-C	129.8	
5-C	153.6	
1'-C	126.8	
2',6'-CH	128.3	8.42(dd, 7.0, 1.2)
3',5'-CH	128.8	7.49(m)
4'-CH	130.7	7.47(m)
CO	161.2	

Example 3

Biological in vitro Activity Bioassays for Antitumour Screening

[0085] The finality of these assays is to interrupt the growth of an "in vitro" tumour cell culture by means a continued exhibition of the cells to the sample to be testing. The following human cell lines were used:

CELL LINES			
Name	N° ATCC	Tissue	Characteristics
K-562	CCL-243	leukemia	myelogenous leukemia (pleural effusion)
A-549	CCL-185	lung	lung carcinoma "NSCL"
SK-MEL-28	HTB-72	melanoma	malignant melanoma
HT-29	HTB-38	colon	colon adenocarcinoma
DU-145	HTB-81	prostate	prostate carcinoma, not androgen receptors
LNCaP	CRL-1740	prostate	prostate adenocarcinoma, with androgen receptors
PC-3	CRL-1435	prostate	prostate adenocarcinoma
BT-474	HTB-20	breast	breast adenocarcinoma
MX-1		breast	breast adenocarcinoma,
Hs746t	HTB-135	gastric	stomach carcinoma
SK-HEP-1	HTB-52	liver	liver adenocarcinoma
SK-OV-3	HTB-77	ovary	ovary adenocarcinoma (malignant ascites)
PANC-1	CRL-1469	pancreas	pancreatic epithelioid carcinoma
5637	HTB-9	bladder	bladder carcinoma
FADU	HTB-43	pharynx	squamous cell carcinoma
786-O	CRL-1932	renal	primary renal cell adenocarcinoma
NCI-H187		SCL	
Y-79	HTB-18	retinoblastoma	retinoblastoma
SW-694	HTB-91	fibrosarcoma	fibrosarcoma
CHSA		chondrosarcoma	chondrosarcoma
OSA-FH		osteosarcoma	osteosarcoma
SK-N-MC	HTB-10	neuroblastoma	neuroepithelioma
TT	CRL-1803	thyroid	medullary thyroid carcinoma
SW-579	HTB-107	thyroid	thyroid carcinoma
HL-60	CCL-240	promyelocytic	leukemia
H9	HTB-176	lymphoma	T-cell-lymphoma
MC116	CRL-1649	lymphoma	lymphoma

Inhibition of cell Growth by Counting Cells

[0086] Tetrazolium Assay MTS is based on metabolic reduction of MTS to solubilized formazan crystals by the metabolically active mitochondria of living cells. For this reason, the methodology includes, counting of the cell lines based on viability staining to ensure that cell concentrations are corrected to allow for 100% living cells into each well in lieu of Coulter counting or estimated dilutions based on standard growth curves.

[0087] Medium containing drug was removed at the end of the treatment and culture plates rinsed one time with PBS. Afterward, cells were incubated in 200 µl of drug-free medium until 72 hours. After appropriate incubation time 25 µl of MTS+PMS solution was added to each microtiter well and incubated for 4 hours at 37° C. Plates were then removed from the incubator and placed on plate shaker for 5 minutes (covered for protection from light). Optical densities were read at 490 nm on spectrophotometer plate reader. Data was analyzed using Softmax.

[0088] Data is presented as IC_{50} potencies calculated from 3rd order polynomial regression curves using Microsoft Excel and then manually interpolated.

[0089] The following table illustrates data on the biological activity of the compounds of the present invention.

Cytotoxic activity (mol/l) of IB-01211		
Bladder	5637	5.79E-7
Breast	BT-474	5.37E-7

-continued

Cytotoxic activity (mol/l) of IB-01211		
Breast	MX-1	5.62E-7
Colon	HT-29	8.17E-7
Gastric	Hs746t	5.92E-7
Liver	SK-HEP-1	6.64E-7
NSCL	A549	9.18E-7
Ovary	SK-OV-3	8.46E-7
Pancreas	PANC-1	4.24E-7
Pharynx	FADU	6.64E-7
Renal	786-O	6.92E-7
Prostate	PC-3	6.21E-7
Prostate	DU-145	4.8E-7
Prostate	LNCAP	6.5E-7
SLC	NCI-H187	2.97E-8
Retinoblastoma	Y-79	9.32E-8
Melanoma	Mel-28	5.08E-7
Fibrosarcoma	SW 694	7.2E-7
Chondrosarcoma	CHSA	5.53E-7
Leukemia/Lymphoma	HL-60	1.41E-7
Leukemia/Lymphoma	K562	6.36E-7
Leukemia/Lymphoma	H9	1.84E-7
Leukemia/Lymphoma	MC116	3.39E-6
Osteosarcoma	OSA-FH	1.2E-7
Neuroblastoma	SK-N-MC	5.31E-7
Thyroid	TT	4.38E-6
Thyroid	SW-579	4.42E-7

Example 4

Biological in vivo Activity

IN VIVO Analysis of BR-0121 in Human Breast, Colon and Non-Small Cell Lung Tumour Xenografts

Tumour Implantation

[0090] At different times, three human tumour cell lines MX-1 (breast), HT-29 (colon), and LX-1 (non-small cell lung), respectively, were implanted subcutaneously into separate groups of recipient female athymic mice as a small seeding of approximately 2-3 mm³. Each tumour type was then allowed to grow inside the animal to reach a group mean size of 100±15 mm³, at which time tumour-bearing mice were randomized into groups (Staging Day). The Staging Day also coincided with Day 0 for drug dosing.

Frequency and Route of Administration of the Test Article

[0091] The test article was administered as a single intravenous (iv) bolus injection (i.e., QDx1) on the Staging Day (Day 0).

Tumour Measurements

[0092] Tumour burden was determined for all animals throughout the study using a caliper, and the frequency was at least twice per week.

Data Analysis

[0093] Protocols and criteria for drug activity were derived from those established by the National Cancer Institute for tumour systems similar to those used in these studies (NIH Publication No. 84-2635. In vivo cancer models 1976-1982). Statistical analysis of tumour volumes for each group of drug treated animals was performed according to the Mann Whitney nonparametric test based on comparisons to the vehicle control cohort within the same experiment.

[0094] Tumour lengths (L) and widths (W) were measured in millimeters (mm) using calipers, recorded, and tumour volume was calculated by the formula: Volume (mm³)=L×W²×0.5. Individual values were determined for each tumour-bearing athymic mouse and specific day of measurement (day D). On the tumour Staging Day (Day 0), the tumour volume of a treated animal (T_{D1}) was subtracted from the corresponding tumour volume on each observation day (T_{D}1). This provided the change (Δ) in tumour volume for the said treated athymic mouse ($\Delta T1=T_{D}1-T_{0}1$). The change in tumour volumes for each treated group of the control cohort (ΔC) was calculated in a similar fashion as above

[0095] Results from tumour xenografts are tabulated below. At randomization (Day 0) the average volume of the tumour mass was 100±15 mm³ and the "net tumour growth" is really a difference between the size of the tumour on Day X and that on Day 0. The parameter S.E.M. is commonly used in statistics and stands for standard error of the mean in a distribution of N (size) experimental values.

[0096] Kinetics of net tumour growth after in vivo administration of BR0121 in human breast tumour (MX-1 cell line) xenografts.

		DAY 3		DAY 6		DAY 10	
TEST ARTICLE	SINGLE DOSE (mg/kg)	Net Tumour Growth ± S.E.M. (mm³)	P Value*	Net Tumour Growth ± S.E.M. (mm³)	P Value*	Net Tumour Growth ± S.E.M. (mm³)	P Value*
Vehicle Control		124 ± 10	---	232 ± 20	---	780 ± 129	---
BR-0121	1.0	5 ± 3 †	0.0652§	113 ± 42 †	0.0232§	450 ± 137 †	0.3811ns
	1.5						---

*P < 0.05, statistically significant (according to the Mann Whitney nonparametric test) given group compared to the Vehicle Control cohort).
§P = 0.05 but <0.075, trend to statistical significance.
† High mortality prevented meaningful statistical analysis.

[0097] Kinetics of net tumour growth after in vivo administration of BR0121 in human colon tumour (HT-29 cell line) xenografts.

		DAY 1		DAY 4		DAY 8	
TEST ARTICLE	SINGLE DOSE (mg/kg)	Net Tumour Growth ± S.E.M. (mm³)	P Value*	Net Tumour Growth ± S.E.M. (mm³)	P Value*	Net Tumour Growth ± S.E.M. (mm³)	P Value*
Vehicle Control	---	7 ± 10	---	46 ± 14	---	126 ± 32	---
BR-0121	0.5	26 ± 12	0.3056	53 ± 28	0.6905	162 ± 34	0.4613

*P < 0.05, statistically significant according to the Mann Whitney nonparametric test given group compared to the Vehicle Control cohort).
N.S., not stated.

[0098] Kinetics of net tumour growth after in vivo administration of IB01211 in human non-small cell lung tumour (LX-1 cell line) xenografts.

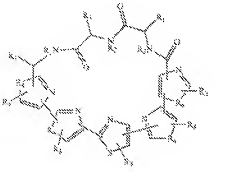
TEST ARTICLE	SINGLE DOSE mg/kg	DAY 2 Net Tumour Growth ± S.E.M. (mm^3)	DAY 2 P Value*	DAY 6 Net Tumour Growth ± S.E.M. (mm^3)	DAY 6 P Value*	DAY 13 Net Tumour Growth ± S.E.M. (mm^3)	DAY 13 P Value*
Vehicle Control	...	106 ± 30	...	303 ± 85	...	467 ± 77	...
IB01211	1.0	68 ± 29	0.0556§	234 ± 41	0.4605	361 ± 60	0.2722
	3.5	11 ± 18	0.0079*	171 ± 53	0.0556§	309 ± 73	0.2222

*P < 0.05, statistically significant (according to the Mann Whitney nonparametric test; given group compared to the Vehicle Control cohort).
§P > 0.05 but <0.06, trend to statistical significance.

[0099] In conclusion, the compound IB01211, with a corresponding maximum tolerated dose (MTD) of 3.5 mg/kg in conventional CD-1 mice, demonstrated significant antitumour effect in vivo against a human non-small cell lung tumour at a dose of 0.43 MTD, and showed a trend to significance against breast tumour at a dose of 0.29 MTD, but not against colon tumour at a dose of 0.14 MTD.

1. A compound of general formula I.

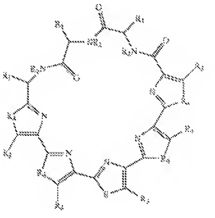
(I)



wherein R_1 are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, nitro, azido, substituted or unsubstituted alkyl, substituted or unsubstituted alkylidene, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group and substituted or unsubstituted acyl, R_2 groups are each independently selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, nitro, azido, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group and substituted or unsubstituted acyl R_3 groups are each independently selected from NR_2, O and S; and R_4 groups are each independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkoxy and substituted or unsubstituted acyl, or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof.

2. The compound according to claim 1, having the following formula II.

(II)



wherein R_1, R_2, R_3 and R_4 are as defined in claim 1

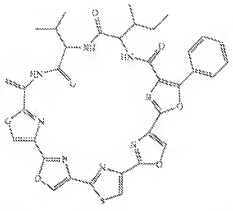
3. The compound according to claim 1, wherein R_1 are each independently selected from substituted or unsubstituted alkyl and substituted or unsubstituted alkylidene.

4. The compound according to claim 1, wherein R_2 are each independently selected from H and substituted or unsubstituted alkyl.

5. The compound according to claim 1, wherein R_4 are each independently selected from H and substituted or unsubstituted aryl.

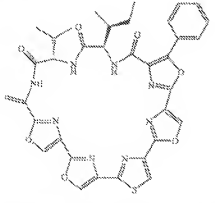
6. The compound according to claim 1, wherein R_3 are each O.

7. The compound according to claim 1 having the following formula



or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof.

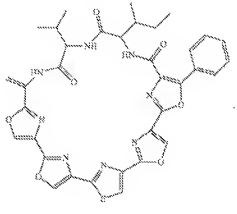
8. The compound according to claim 7, having the following stereochemistry



9. A process for producing a compound as defined in claim 1 which comprises synthesising a oxazole/thiazole/imidazole fragment, and introducing an aminoacidic fragment.

10. A process for preparing a compound as defined in claim 1 which comprises cultivating a strain of a microorganism capable of producing it.

11. A process according to claim 10, wherein the compound prepared is ES-01211 of formula



12. A process according to claim 10, wherein the microorganism is an actinomycete.

13. A process according to claim 12, wherein the microorganism is the substantially pure culture strain ES7-098, available under accession number CECT 3338, from the Colección Española de Cultivos Tipo in the University of Valencia, Spain.

14. A pharmaceutical composition comprising a compound as defined in claim 1, or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof, and a pharmaceutically acceptable diluent or carrier.

15. (canceled)

16. (canceled)

17. A method of treatment of cancer which comprises administering an effective amount of a compound as defined in claim 1, or a pharmaceutically acceptable salt, derivative, prodrug or stereoisomer thereof.

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